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Adaptive working memory strategy training in early Alzheimer's disease: randomised controlled trial

J. D. Huntley, A. Hampshire, D. Bor, A. Owen and R. J. Howard

Background

Interventions that improve cognitive function in Alzheimer's disease are urgently required.

Aims

To assess whether a novel cognitive training paradigm based on 'chunking' improves working memory and general cognitive function, and is associated with reorganisation of functional activity in prefrontal and parietal cortices (trial registration: ISRCTN43007027).

Method

Thirty patients with mild Alzheimer's disease were randomly allocated to receive 18 sessions of 30 min of either adaptive chunking training or an active control intervention over approximately 8 weeks. Pre- and post-intervention functional magnetic resonance imaging (fMRI) scans were also conducted.

Results

Adaptive chunking training led to significant improvements in verbal working memory and untrained clinical measures of general cognitive function. Further, fMRI revealed a bilateral reduction in task-related lateral prefrontal and parietal cortex activation in the training group compared with controls.

Conclusions

Chunking-based cognitive training is a simple and potentially scalable intervention to improve cognitive function in early Alzheimer's disease.

Declaration of interest

None.

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Alzheimer's disease, the most common form of dementia, is characterised by progressive impairment in multiple cognitive domains, including episodic memory and working memory.¹ Working memory capacity is limited to only a few items of information,² consequently humans use executive strategies, such as chunking, to enable working memory to hold complex mental representations. Chunking refers to the process of recognising or enforcing patterns upon information, and compressing it into a more efficient state, thereby creating complex 'chunks' of information that can be held within the limited capacity working space of working memory. The ability to use chunking is preserved in the early stages of Alzheimer's disease,¹ potentially providing a promising target for effective cognitive training in Alzheimer's disease.³ Cognitive training involves the use of theoretically driven exercises targeting specific cognitive domains in order to optimise cognitive function.⁴ Cognitive training can lead to improvements in the cognitive tasks and domains specifically trained in healthy people,⁵ and there is growing evidence that working memory training can lead to generalised improvements in non-trained tasks,⁶ particularly tasks that depend on working memory and the control of attention.⁷ Evidence for the efficacy of working memory training in Alzheimer's disease, however, has so far been limited.⁸ Furthermore, cognitive training studies in Alzheimer's disease rarely apply the rigorous control interventions required for a formal clinical trial.⁹

Successful generalisation of cognitive training benefits to non-trained tasks may have a basis in altered processing within 'domain general' neural systems that make a broad contribution to cognition. Animal and human studies have demonstrated that encoding, storage and retrieval of information in working memory is associated with activity in the prefrontal cortex (PFC) and posterior parietal cortex (PPC).^{10,11} Several groups

have identified activation in the PFC and left PPC accompanying the executive control of information within verbal working memory.¹² This network is also associated with a range of higher-level executive processes,¹³ including the successful use of chunking strategies.^{14,15} Consequently, effective cognitive training may be associated with training-induced plasticity in this common prefrontal-parietal network⁷ and chunking has been postulated as a major strategy underlying these successful cognitive training regimes.¹⁶ We conducted a parallel randomised controlled trial to investigate whether training individuals with early Alzheimer's disease using an adaptive chunking working memory task would improve their working memory capacity. We hypothesised that training-related improvements in working memory capacity would generalise across different modalities of working memory tasks, as well as measures of general cognitive functioning and executive function, and that these improvements would be accompanied by evidence of plasticity of functional activity in the PFC and parietal cortex.

Method

A total of 30 participants with early Alzheimer's disease (according to NINCDS-ADRDA criteria¹⁷) were recruited from memory services of the South London and Maudsley NHS Foundation Trust. Of these, 27 had diagnoses of probable Alzheimer's disease and 3 had diagnoses of possible Alzheimer's disease, having recently converted from mild cognitive impairment to Alzheimer's disease. Diagnoses were made by experienced old age psychiatrists unconnected to the study. Inclusion criteria were a Mini-Mental State Examination (MMSE) score of >22/30 and age >60 years (see online supplement DS1 for further details). Exclusion criteria included coexistent neurological or psychiatric disease, substance

misuse or significant auditory or visual impairment. All participants had capacity to provide written informed consent to participate in the study, which was approved by the NRES Committee East of England-Cambridge East (REC reference number 10/H0304/68) and registered prior to the onset of the study (trial number: ISRCTN43007027). Following informed consent and baseline functional magnetic resonance imaging (fMRI), participants were randomised to either training ($n=15$) or control groups ($n=15$) using an online block randomisation program.

Outcome measures

The primary outcome measure was a computerised verbal working memory span task, involving both structured (chunkable) and random sequences (see online Fig. DS1). Structured trials consisted of digits presented in runs of consecutive numbers or numbers increasing or decreasing in 2s or 3s (for example, 2,4,6,8 or 9,7,5,1,2,3). Previous studies have demonstrated that structured trials significantly encourage chunking, lessening working memory demand and significantly improving working memory performance.^{14,15} Near transfer of training effects to untrained working memory tasks was assessed using a spatial span task. Both structured and random versions of the task were used, with structured trials consisting of consecutive blocks presented in the same row or column, or in recognisable shapes. In the random version of these tasks, number sequences or blocks were presented in random combinations.

Transfer of training effects to clinical measures of general cognitive function were examined using the MMSE and Alzheimer’s Disease Assessment Scale – Cognitive Section (ADAS-Cog). Transfer of training effects to episodic memory was assessed using the Logical Memory II task and Paired Associates Learning task (PAL). Transfer of training effects to executive function was assessed using a verbal fluency task, trail making tasks A and B and computerised grammatical reasoning, ‘odd one out’ and ‘self ordered search’ tasks. See online supplement DS1 for descriptions of all tasks and statistical analyses.

fMRI

All participants underwent pre- and post-intervention fMRI on a Siemens 3T scanner. While undergoing fMRI, participants performed a five-digit span working memory task adapted for people with Alzheimer’s disease from a previous fMRI study in young healthy individuals,¹⁵ requiring them to encode, retain and then verbally recall the five digits in order. Three blocks of twenty trials were performed and structured or random span sequences were presented pseudo-randomly. See online supplement DS1 for details of fMRI acquisition and analysis.

Interventions

Participants randomised to the training group underwent 18 sessions of training over approximately 8 weeks, in line with recent studies demonstrating effective cognitive training interventions.¹⁶ Each session consisted of 30 trials of an adaptive structured digit span task. The initial span length was a three-digit sequence, presented on a computer screen. If the participant correctly recalled the sequence, then the number of digits to be recalled (span) would increase by one for the subsequent trial. Conversely, if the sequence was incorrectly recalled, the next trial would have one fewer digits. In this way participants reached and then oscillated around their maximum span, which could adapt to performance both within and across training sessions. Control participants underwent 18 sessions of an active control intervention involving 30 trials of a fixed, non-adaptive unstructured three-digit span task. This controlled for most aspects of the experimental intervention, apart from the adaptive chunking elements.

Results

The study was conducted between February 2011 and August 2014. All participants completed the study (see online Fig. DS2). Analysis of baseline demographic information demonstrated no significant differences between the groups on any of the demographic or screening variables (see online Table DS1). The mean or median scores and standard deviations or interquartile ranges for each group at pre- and post-intervention, and effect

| Table 1 Pre- and post-scores and effect sizes of all cognitive outcomes ^a | Training group ($n=15$) | | Control group ($n=15$) | | Effect size, | |
|--|---------------------------|-------------------|-----------------------------------|--------------------|--------------|--------------|
| | Pre | Post | Pre | Post | r | P |
| Working memory, mean (s.d.) | | | | | | |
| Digit span structured trial | 5.49 (0.92) | 6.30 (0.90) | 5.53 (0.90) | 5.79 (0.75) | 0.42 | 0.017 |
| Digit span random trial | 5.23 (0.84) | 5.64 (0.85) | 5.01 (0.88) | 5.33 (0.69) | 0.08 | 0.670 |
| Spatial span structured trial | 3.83 (1.05) | 3.98 (0.66) | 3.90 (0.70) | 4.04 (0.82) | 0.01 | 0.959 |
| Spatial span random trial | 3.62 (0.91) | 3.74 (0.59) | 3.56 (0.75) | 3.74 (0.85) | −0.05 | 0.777 |
| General cognitive function | | | | | | |
| Mini-Mental State Examination, mean (s.d.) | 26.00 (2.30) | 26.10 (2.00) | 25.93 (2.09) | 24.60 (1.84) | 0.44 | 0.011 |
| ADAS-Cog, median (IQR) ^b | 11.00 (9.66–18.33) | 8.67 (6.33–15.33) | 13.00 (9.66–17.66) | 14.66 (13–15) | −0.58 | 0.001 |
| Episodic memory, mean (s.d.) | | | | | | |
| Logical Memory Task 2 | 7.20 (8.20) | 12.47 (8.27) | 7.93 (7.05) | 7.73 (8.06) | 0.51 | 0.003 |
| Paired Associates Learning task, median (IQR) | 3.00 (3–4) | 3.00 (3–3) | 3.00 (3–3) | 3.00 (2–4) | −0.33 | 0.075 |
| Executive function | | | | | | |
| Verbal fluency, mean (s.d.) | 8.64 (2.73) | 8.00 (2.59) | 8.21 (2.52) ^c | 8.27 (2.43) | −0.11 | 0.577 |
| Grammatical reasoning, mean (s.d.) | 6.00 (5.28) | 5.40 (4.40) | 4.73 (4.59) | 6.80 (5.72) | −0.32 | 0.074 |
| Odd one out, mean (s.d.) | 10.20 (3.10) | 9.40 (3.42) | 7.60 (2.29) | 8.53 (3.02) | −0.25 | 0.162 |
| Self ordered search, median (IQR) | 4.00 (4, 6) | 5.00 (4, 6) | 4.00 (3, 5) | 5.00 (4, 6) | −0.28 | 0.121 |
| Trail making task part A, median (IQR) | 52 (33–115) | 66 (38.4–199.00) | 63.50 (44.75–112.25) ^c | 65.5 (41.25–96.25) | −0.11 | 0.556 |
| ^a . Scores for Alzheimer’s Disease Assessment Scale – Cognitive section (ADAS-Cog), Paired Associates Learning task, self ordered search task and trail making task part A are shown as medians and interquartile ranges (IQR), as data were not normally distributed. The units are maximum scores for all tasks except trails A (time in seconds), fluency (maximum of 14), Logical Memory Task 2 (maximum of 32). Results of trail making task, part B are not reported due to floor effects at both time points. Results in bold are significant. | | | | | | |
| ^b . The ADAS-Cog is inversely scored, therefore higher scores represent more impairment. | | | | | | |
| ^c . $n=14$. | | | | | | |

sizes for all primary and secondary behavioural outcome measures are shown in Table 1.

The primary outcomes were the mean digit span scores on structured and random trials (Fig. 1). Repeated measures ANOVA with PrePost (pre *v.* post) and chunking (structured *v.* random trials) as within-participants factors and group as the between-participants factor, revealed a significant main effect of PrePost ($F(1,28) = 26.282$, $P < 0.001$), indicating that both groups improved on the digit span task over the course of the study, and a main effect of chunking ($F(1,28) = 58.605$, $P < 0.001$), demonstrating that both groups performed significantly better on structured compared with random trials (Fig. 1). The interaction between PrePost, chunking and group neared significance ($F(1,28) = 4.067$, $P = 0.053$). The basis of this complex interaction was examined by performing separate repeated measures ANOVAs for each trial type, with PrePost as the within-participants factor and group as the between-participants factor.

Analysis of the structured trials revealed a significant main effect of PrePost ($F(1,28) = 24.07$, $P < 0.001$) and a significant PrePost \times group interaction ($F(1,28) = 6.40$, $P = 0.017$). Paired *t*-tests were subsequently conducted as *post hoc* analyses to investigate the PrePost \times group interaction. The control group demonstrated a non-significant increase in structured span score ($P = 0.115$), however, the training group significantly improved in structured span score following training ($P < 0.001$). This equated to a mean

difference in change score (post–pre) on the structured span between the groups of 0.55 (95% CI 0.11–1.00, $r = 0.42$). Analysis of random trials revealed a significant main effect of PrePost ($F(1,28) = 13.025$, $P = 0.001$) but no other significant main effects or interactions.

Secondary behavioural outcomes were performance on random and structured versions of the spatial span task, and scores on measures of general cognitive function, episodic memory and executive function. Repeated measures ANOVA of spatial span scores, demonstrated no significant main effects of PrePost or group. The main effect of chunking was significant ($F(1,28) = 24.044$, $P < 0.001$), with participants performing significantly better on structured compared with random trials. There were no significant interactions between PrePost and group or PrePost \times chunking \times group, indicating no significant transfer effects of training to spatial span.

Repeated measures ANOVA examining MMSE score revealed a significant main effect of PrePost ($F(1,28) = 5.467$, $P = 0.027$) and a significant interaction between PrePost and group ($F(1,28) = 7.383$, $P = 0.011$). Results are shown in Table 1 and Fig. 2.

The ADAS-Cog data were not normally distributed, therefore post–pre change in ADAS-Cog scores were calculated for each participant and a Mann–Whitney *U*-test was conducted. This revealed a significant difference between the groups ($U = 36$, $z = -3.175$, $P = 0.001$ (2-tailed)). Related sample Wilcoxon rank tests were therefore performed for each group. The control group demonstrated a non-significant increase in ADAS-Cog score ($z = -1.412$, $P = 0.158$), reflecting a deterioration in cognitive function, while the training group significantly decreased in score ($z = -2.670$, $P = 0.008$), representing an improvement in cognitive function following training.

Repeated measures ANOVA of logical memory score revealed a significant main effect of PrePost ($F(1,28) = 4.516$, $P = 0.043$), and no significant main effect of group. There was a significant interaction between PrePost and group ($F(1,28) = 10.506$, $P = 0.003$), demonstrating a significant training-related improvement in verbal episodic memory function (Fig. 2). The PAL data were not normally distributed. Therefore, post–pre change in PAL scores were calculated and a Mann–Whitney test was conducted, which revealed no significant difference between the groups ($U = 71.5$, $z = -1.783$, $P = 0.075$ (2-tailed)).

Individual repeated measures ANOVAs, with time as the within-participants variable and group as the between-participants variable were conducted on the fluency, grammatical reasoning and odd one out tasks. There were no significant main effects or interactions on any of the executive function tasks. Similarly, Mann–Whitney tests, with post–pre change score as the test variable revealed no significant differences between the groups on the trails A or self ordered search tasks. The trail making test part B data were not analysed due to floor effects, as 18 participants failed to complete the task.

A fixed five-span digit span task was performed in both pre- and post-intervention fMRI sessions. Repeated measures ANOVA demonstrated a significant effect of chunking on performance ($F(1,28) = 6.871$, $P = 0.014$). Both groups correctly recalled more structured than random trials at both pre- (72.1% structured trials correct *v.* 68.6% random trials correct) and post-intervention (76.3% *v.* 71.6%). There were no other significant main effects or interactions.

The fMRI analyses followed an *a priori* region of interest (ROI) approach based on the hypothesis that training-related improvements would be accompanied by plasticity in the functional activity of PFC and parietal cortex areas involved in the task. ROIs were defined as 10 mm spheres around central

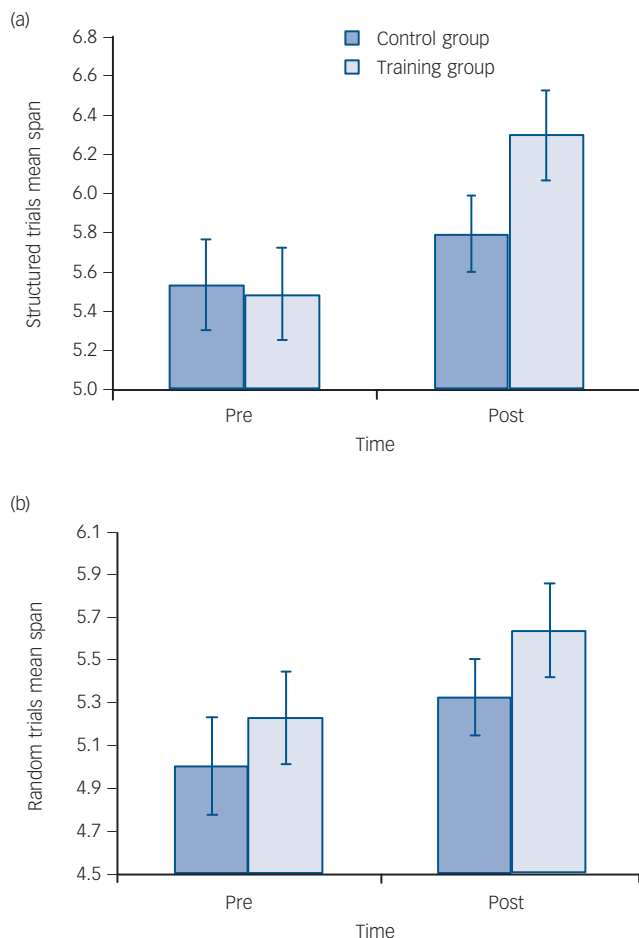


Fig. 1 Mean digit span scores on structured and random trials.

(a) Mean digit span score on structured trials at pre- and post-intervention; (b) mean digit span scores on random trials at pre- and post-intervention. When each trial type is examined separately there is a significant main effect of time for both trial types ($P < 0.001$) and a significant time \times group interaction ($F(1,28) = 6.40$, $P = 0.017$) for structured trials (a), but not for random trials ($P = 0.67$) (b). Error bars are standard errors of mean.

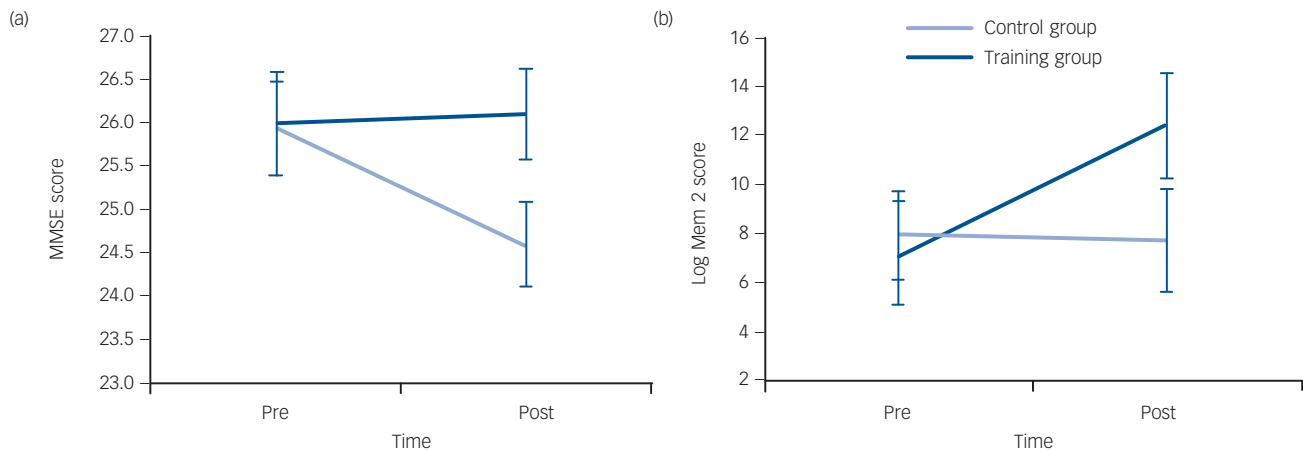


Fig. 2 Mean scores pre- and post-interventions on (a) Mini-Mental State Examination (MMSE) and (b) Logical Memory Task 2 (Log Mem 2) tasks.

Error bars are standard errors of mean. Time \times group interactions are all significant (MMSE $P=0.011$ and Log Mem 2 $P=0.003$).

coordinates in the right dorsolateral prefrontal cortex (DLPFC) (39, 43, 33), left DLPFC (−39, 36, 36), right parietal cortex (46, −40, 42) and left parietal cortex (−37, −45, 37). The parameter estimates produced from each of the factors in the model were summarised across all voxels within each ROI and these values were entered into a repeated measures ANOVA. Within-participant factors were PrePost (pre *v.* post), chunking (structured *v.* random), ROI (DLPFC *v.* parietal cortex) and hemisphere (right *v.* left), with group as the between-participants factor. There were no significant main effects, however, there were significant complex interactions between PrePost \times ROI \times hemisphere \times group ($F(1,27) = 4.232$, $P = 0.049$), PrePost \times chunking \times ROI \times hemisphere ($F(1,27) = 6.989$, $P = 0.013$), PrePost \times chunking \times hemisphere ($F(1,27) = 5.422$, $P = 0.028$) and a near significant overall interaction between PrePost \times group ($F(1,27) = 3.899$, $P = 0.059$). To further determine the basis of these interactions, separate repeated measures ANOVAs were conducted for each trial type. For structured trials there was a significant interaction of PrePost \times group ($F(1,27) = 5.403$, $P = 0.028$), a significant PrePost \times ROI \times hemisphere \times group interaction ($F(1,27) = 5.030$, $P = 0.033$), and no other significant main effects or interactions. For random trials there was a significant ROI \times hemisphere interaction ($F(1,27) = 4.562$, $P = 0.042$), and no other significant main effects or interactions. To further examine the significant training effects for structured trials further ANOVAs were conducted for each ROI individually.

In the right DLPFC there was a significant PrePost \times group interaction ($F(1,27) = 4.422$, $P = 0.045$), but no main effects of PrePost or group (Fig. 3 and online Fig. DS3(a)). In the left DLPFC there were no significant main effects and no significant effect of training (PrePost \times group interaction ($F(1,27) = 2.735$, $P = 0.110$)). In the left parietal cortex there was a significant PrePost \times group interaction ($F(1,27) = 4.604$, $P = 0.041$) and no significant main effects. In the right parietal cortex the PrePost \times group interaction neared significance ($F(1,27) = 4.072$, $P = 0.054$) and there were no significant main effects of PrePost or group (Fig. 3 and online Figs DS4(a) and (b)). These results all demonstrated a similar pattern of training-related reduced activation in all four ROIs as a result of training compared with increased activation in all four regions in the control group. However, the reliability of the effects varied significantly across the frontal and parietal ROIs (Fig. 3).

Whole brain analyses were also conducted to identify any additional voxels or voxel clusters that significantly changed in

level of activation, other than the defined ROIs. Examining for training effects (PrePost \times group, and PrePost \times chunking \times group contrasts), revealed no additional significant voxels when corrected for multiple comparisons using family-wise error during either encoding or delay.

Discussion

Main findings

This randomised controlled trial demonstrated that 18 sessions of adaptive working memory training in verbal chunking strategies given to patients with Alzheimer's disease, led to significant performance improvements on the trained verbal working memory task, and also to improvements on general cognitive and verbal episodic memory outcomes. Further, the observed cognitive benefits were accompanied by evidence of change in the functional activity of cortical networks that are known to be involved in the task. Although training led to improvements compared with the control group on the MMSE and ADAS-Cog (both clinical measures of general cognitive function), there was no transfer of benefits to non-verbal working memory or episodic memory tasks, or to specific measures of executive function. This apparent discrepancy can be resolved if it is assumed that there was no improvement in intelligence or executive function *per se* as a consequence of training. Instead, training on this digit-based chunking task may have only increased the application of verbal recoding strategies in other tasks. Indeed, generalised benefits were only seen on those tasks that were amenable to the adaptive use of similar chunking strategies. For example, both the story recall in the logical memory task and word recall lists of the ADAS-Cog could potentially be chunked, based on linguistic or verbal-semantic links between test items.

Interpretation of fMRI results

The consistent pattern of training-related plasticity seen in the brains of participants was of a decrease in functional activity in all ROIs following training. This was in contrast to increased activation in all examined ROIs in control participants between the baseline and follow-up scans. This pattern of results is consistent with a growing literature reporting that cognitive training leads to a decrease in cortical functional activity.¹⁸ Initially a task may require large attentional and executive resources in order to be successfully performed. This executive

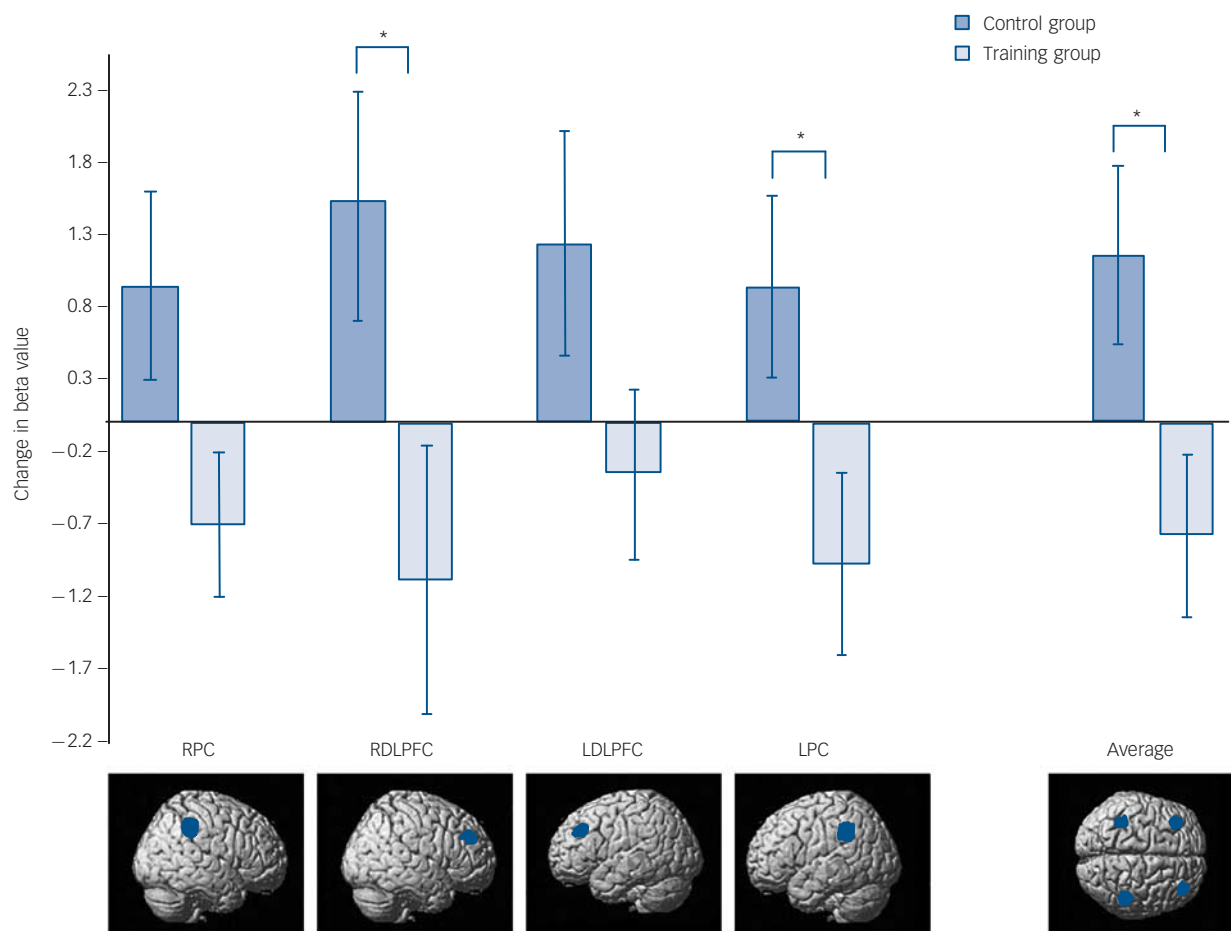


Fig. 3 Results of the change in functional magnetic resonance imaging (fMRI) response (calculated as post-beta value – pre-beta value), in each of the four specified regions of interest.

Right parietal cortex (RPC, 46, –40, 42), right dorsolateral prefrontal cortex (RDLPFC 39, 43, 33), left dorsolateral prefrontal cortex (LDLPFC –39, 36, 36), left parietal cortex (LPC –37, –45, –37), Average, change in beta values averaged across all four regions of interest. Error bars are standard errors of mean.
*group difference significant at $P < 0.05$.

resource may be underpinned by a ‘scaffold’ of cortical regions, including the PFC and PPC.^{18,19} As training continues, the requirement for attentional and executive resources diminishes, and therefore activation in this network correspondingly decreases as the ‘scaffolding falls away’.^{18,19} A number of potential neurobiological mechanisms at the synaptic, neuronal and neural network level may be important in such ‘scaffolding’ and efficiency.

Several studies examining the effects of practice have described a decrease in cortical activation within the course of a single session.^{18,20} This suggests that functional redistribution can occur over short timescales of around an hour. However, in keeping with the current study, other studies have also demonstrated similar redistribution dynamics that developed over longer training periods of several weeks.⁶

The initial increase in activation in the PFC–PPC network predicted by the scaffolding/efficiency theory may also explain the results observed in control participants. The active control intervention was a low-level cognitive demand task of only three digits. Therefore, the five-digit span task performed in the scanner would represent a considerable increase in task difficulty from the control intervention. In keeping with this theory, control participants would require increased executive resources to perform the five-digit task, which would be reflected in increased PFC–PPC activity, in contrast to the participants in the training

group, who had been adaptively trained. However, while this may explain an increase in activity in the PFC–PPC in untrained participants performing the working memory task, the observation that the activation in control participants increased from baseline to follow-up, rather than remaining at a constant level, needs to be explained. It has been observed that, in line with the efficiency theory, activation in PFC and PPC areas may follow an inverted U-shaped quadratic function, with activity increasing early in training, prior to decreasing.²¹ It is possible that control participants, due to the low-level training they had received, were still at a point near the top of the inverted U-shaped curve, and that adaptive training led to participants in the training group being much further along the curve, so that decreasing activation was observed.²¹ It may also be possible that the increase in activity reflects the improved span performance seen in controls, as they may have been more engaged and trying harder at the task at follow-up compared with their baseline exposure to fMRI.

Critically, however, the current study provides evidence of the potential for functional plasticity following training in an Alzheimer's population. Functional plasticity is increasingly reported in older adults and in mild cognitive impairment;²² however, the extent to which training-related plasticity may be possible in Alzheimer's disease remains unclear. These findings provide important and encouraging support for the presence of continued plasticity in the early stages of dementia.

Strengths and limitations

Limitations of this study include the small number of participants, and it is possible that the study was underpowered to find further areas of significant improvement or plasticity on fMRI. The study, although randomised and well controlled, was not blinded. Therefore, observer bias may be present in the behavioural outcome measures, although attempts were made to avoid this through the use of computerised tasks and validated outcome measures.

This study also demonstrated that computerised working memory training was acceptable to participants with Alzheimer's disease and their carers. Once training had commenced, no participants dropped out of the study, despite the considerable commitment required. Anecdotally, participants enjoyed engaging with the training and control interventions and felt empowered that they were investing in a potentially useful exercise. This reflects the significant public and patient interest in cognitive training, which has become a billion dollar industry; however, there remains a clear need for the efficacy of cognitive training tools to be assessed in well-controlled randomised trials in patients with Alzheimer's disease. The observed benefits of adaptive chunking training in the verbal domain should be broadened in future studies focusing on exploring the utility of this method. For instance, benefits of strategy training could be tracked in the longer term, and similar training in other domains such as object- or spatial-based working memory could be explored. The ability of patients with mild Alzheimer's disease to access and engage with computerised cognitive training tools presented online also needs further investigation, as this approach would enable cognitive training to be made widely available in a cost-effective manner.

Worldwide, in 2013 there were 44.4 million people with Alzheimer's disease, projected to rise to 135.5 million by 2050.²³ Any tool that could help this very large and highly disabled clinical population would have a profound positive effect on society. We have here described one such potential tool, chunking-based cognitive training, which could be an effective future technique to help maintain cognitive function in early Alzheimer's disease.

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Online supplement DS1

Participants

Thirty participants with early AD were recruited from memory and community health services of the South London and Maudsley NHS Foundation Trust. Diagnoses were made by Old Age Psychiatrists and multidisciplinary teams unconnected to the study. Twenty-seven participants had a diagnosis of 'probable' AD (according to NINCDS-ADRDA criteria ¹) and 'Dementia in Alzheimer's Disease (F00)' according to ICD-10 criteria ². Three participants (two training and one control participant) had a diagnosis of 'possible' AD, having been assessed as converting from mild cognitive impairment (MCI) to AD within the preceding 8 weeks. We acknowledge that patients at this very early stage of AD may overlap with the criteria for Mild Cognitive Impairment on objective cognitive assessment, however diagnoses were made by clinical teams based on the history of functional and cognitive deterioration and progression. For the purpose of this study 'early AD' was defined as a diagnosis of AD with mild cognitive and functional impairment, rather than indicating a recent diagnosis or early-onset of dementia. The inclusion criteria therefore stated that baseline MMSE³ was required to be >22/30 in order to recruit participants at the earliest stage of AD, where cognitive impairment remained mild. All baseline scores on cognitive assessments are shown in Table 1. The mean length of time between diagnosis of AD being made and recruitment into the trial was 419.7 (591.76) days for the control group and 545.29 (513.42) days for the intervention group (see online Table DS1). Although the inclusion criteria allowed patients with age > 60 to be considered for the study, participants ages ranged from 65 to 88 years, and no participant had a diagnosis of Alzheimer's disease with early-onset (see online Table DS1).

Secondary outcome measures

Transfer of training effects to clinical measures of general cognitive function were examined using the mini mental state examination (MMSE)³ and Alzheimer's disease assessment scale- cognitive section (ADAS-Cog)⁴. The MMSE is a clinically widely used 30-point pen-and-paper test incorporating assessments of orientation (10 points), immediate and delayed recall (6 points), reading, repetition, writing and copying of a shape (4 points), object recognition (2 points), following a three-stage instruction (3 points) and attention (5 points). Points are scored for each correct response, with a maximum score of 30. The ADAS-Cog is a widely used 70 point pen-and-paper assessment involving eleven subsections that evaluate word recall, word finding and naming, following commands,

orientation, copying shapes, performing a 5 stage task, recall of test instructions, word recognition, spoken language ability and language comprehension. It is reverse scored, therefore higher scores represent greater cognitive impairment.

Transfer of training effects to non trained cognitive domains were assessed using the Logical Memory I+II tasks and Paired Associates Learning task (PAL) to assess episodic memory. The logical memory I+II is a verbal episodic memory task and is taken from the Wechsler Memory Scale ⁵. Participants were read a short story and asked to remember it. They were then asked to immediately recall as much of the story as possible (part I). After 25 minutes they were asked to recall the story again (part II). Each part is scored for 25 specific and 7 thematic components, with a total score of 32 points.

The PAL task examines visuo-spatial episodic memory and is sensitive to episodic memory deficits in early AD ⁶. A number of boxes were presented at different locations on a computer screen. Each box covered a picture. The boxes were initially shown, followed by the pictures under each box. Each picture was then presented in the middle of the screen and the participant had to recall which picture appeared under which box, therefore testing both object and location recall. If a participant correctly recalled all the pictures, the next set of boxes had one more box/picture combination. If an error was made a new set of boxes was presented, with one fewer box/picture. If 3 errors were made, the task ended.

Transfer of training effects to executive function was assessed using the following tasks:

1) Verbal Fluency task ⁷: Participants were asked to generate as many words as they could, beginning with the letter P in one minute, not including place or person names. They were then asked to generate as many types of animal they could in one minute, whose name began with any letter of the alphabet. The total number of words generated for each category was converted to a score out of 7 (> 17 words = 7, 14-17 words = 6, 11-13 words = 5, 8-10 words = 4, 6-7 words = 3, 4-5 words = 2, 2-3 words = 1, < 2 words = 0), with a maximum total score of 14 for the two tasks.

2) Grammatical Reasoning Task⁸: In this task a picture of a square and circle were presented on a computer screen.

A sentence describing the relationship between the circle and square was presented above the picture and the participant had to choose whether the sentence describing the picture was true or false. The participant had 90 seconds to answer as many true/false questions as they could.

3) Odd One Out task⁹: In this task a 3 x 3 grid of objects were presented on a computer screen. Each object was made of up of one or multiple shapes or colours. One object differed from all of the others, owing to it being a different shape, combination of parts or colour. The participant had to select which object they thought was the 'odd one out'. The participant had 3 minutes to answer as many trials as possible in the time.

4) Trail Making tasks A and B¹⁰. In Task A, participants were asked to connect a series of numbered circles on a piece of paper as quickly as possible. In Task B, participants were again asked to connect a series of circles containing ascending numbers or letters of the alphabet. On this occasion they were asked to alternate between numbers and letters (e.g. 1-A-2-B-3-C etc) and connect up all of the circles as quickly as possible. Prior to doing the task, participants were given short practice examples to complete. If an error was made, the examiner was allowed to point this out to the participant for them to correct. Each part was timed, and a time to completion for each part of the task was recorded. If the combined time was > 300s the task was discontinued¹¹. Results of part B are not reported as 7/15 control participants and 11/15 training participants were unable to complete the task at baseline.

5) Self Ordered Search task⁹: In this task a series of boxes were presented on a screen. The aim was to search through the boxes in order to find a gold coin hidden in one of the boxes. Gold coins appeared sequentially in the boxes, with a new coin appearing in one of the remaining boxes after each coin had been found. There were two rules to the task. Firstly, a coin was never hidden in the same box twice; therefore if a coin had already been found in a box, and the participant looked in that box again, they lost a "life". Secondly, if a participant looked in the same empty box twice whilst looking for a coin, they lost a "life". The task proceeded with the participant deciding which boxes to look in, and continued until a gold coin has been found in each box. If an error was made, the participant lost a "life" and a new trial started with one less box. If the participant successfully found all the gold coins, a new trial began with one additional box. The task therefore tested the participant's ability to plan and execute a strategy and also recall the spatial location of boxes searched and coins previously found.

Statistical analyses

For the primary outcome measures, mean span accuracy scores were analysed using a mixed repeated measures analysis of variance (ANOVA) in statistical Package for the Social Sciences (SPSS v 22.0)¹². In these analyses time (pre vs post intervention) and trial type (structured trials vs random trials) were within subjects factors, and group (training vs control) was the between subjects factor. If there was evidence of significant time x group, or time x trial type x group interactions, these were then further explored by further repeated measures ANOVAs for each trial type separately and paired T tests for each group separately.

For the secondary outcome measures, maximum scores were analysed using mixed repeated measures ANOVAs with time (pre vs post intervention) as the within subjects factor and group as the between subjects factor. The effect of training on primary and secondary outcomes was also examined by calculating change scores (post –pre) and effect sizes (r). Assumptions of parametric data were assessed for all data. If the assumptions of parametric data were violated, Mann–Whitney and Wilcoxon signed-rank non parametric tests were conducted. For all analyses the α significance level was set at 0.05.

fMRI acquisition

All participants underwent pre and post intervention fMRI on a Siemens 3T scanner, at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, London. The mean duration between pre and post scan for all participants was 82.97 (28.11) days, with no significant difference between groups. Functional images were collected with an EPI sequence using an event-related design sequence (8-channel head coil, 30ms TE, 2s TR, 75 deg. flip angle, 64-by-64 matrix, FOV 21.1cm (such that the voxel size is isotropic 3.3mm³), 4 DDAs, 246 volumes). Whilst undergoing fMRI, participants performed a 5-digit span WM task adapted for AD subjects from a previous fMRI study of young healthy individuals¹³, requiring them to encode, retain and then verbally recall the 5 digits in order. The task difficulty at both baseline and post intervention fMRI sessions was fixed at 5 span in order to control for performance differences between the fMRI sessions. Any observed changes in activation between fMRI sessions would therefore be due to effects of the intervention, rather than due to confounding effects of differential task difficulty or performance during scanning sessions. Three blocks of twenty trials were performed and structured or random span sequences were presented pseudo-randomly.

fMRI analysis

Structural MPRAGE images were registered to a template generated from the mean of all participants, using the DARTEL toolbox in SPM8¹⁴. Individual participant functional data was corrected for slice timing, realigned for motion and co-registered to the participant specific structural image. Data were normalised to MNI space using the DARTEL structural template and individual participant flow fields. One participant was excluded from imaging analysis due to incomplete structural imaging data. In the first level analysis, events of interest were parameterised to ensure orthogonal contrasts. Structured trials, random trials and all incorrect responses at the encoding, maintenance and recall stages were included as regressors in the design matrix, along with 6 movement regressors. If there was excessive movement between images, (defined as > 4mm or 5 degrees of rotation), these images were included as an additional regressor of no interest. The specified time series of events were convolved with the haemodynamic response to create predictor functions. These were fitted to time BOLD series at each voxel using the General Linear model in SPM8 along with six movement parameters. The high pass filter was set to 128s to remove low-frequency drifts in signal.

Random effects analysis was conducted on group-level data. A 2 x 2 x 2 full factorial design was used with PrePost (pre vs. post) and Chunking (structured trials vs. random trials) as within subjects and group as the between subjects factor.

A region of interest (ROI) approach was applied based on the *apriori* hypotheses that the structured WM task would be associated with prefrontal and parietal activation, as had been found in previous studies in young healthy adults. Bilateral prefrontal cortex and parietal cortex ROIs were defined from the study group data set to allow for the anticipated structural and task related functional differences between AD participants used in the current study and healthy young populations examined in previous studies^{13, 15, 16}. In order to avoid selection bias, the SPM of the whole brain positive effect of condition contrast (overall performance of WM task) was used to define ROIs as this contrast was orthogonal to the contrasts of interest (pre vs post intervention and structured vs random trials).

Regions of interest were defined using the MarsBar toolbox in SPM8, and estimated beta values were extracted, winsorised, (replacing any values mean \pm 2.5 x SD with that value), and analysed in SPSS using a repeated measures ANOVA. All fMRI data were processed and analysed using SPM8 software 2011.

As the study included an fMRI paradigm, the sample size was calculated from previous studies using a similar paradigm which produced significant results in healthy controls with group sizes of $n = 14$, producing effect sizes of

0.9 and 1.7^{13,15}. Recent cognitive training studies have yielded significant results in controls with group sizes of n = 8 producing an effect size of 1.75¹⁷. Based on these studies, power calculations gave 80% power to detect a significant difference (p<0.05) with group sizes of > 12.

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Table DS1 Demographic and screening variables

| | CONTROL (n = 15) Mean (SD) | TRAINING (n = 15) Mean (SD) | Sig (p) |
|--------|----------------------------------|-----------------------------------|--------------------|
| AGE | 80.13 (5.19) | 79.40 (6.19) | 0.728 |
| MMSE | 25.93 (2.09) | 26.00 (2.30) | 0.934 |
| YRS ED | 12.57 (2.82)* | 12.33 (2.94) | 0.832 [†] |
| IQ | 115.63 (6.78) | 117.14 (6.80) | 0.548 |
| GDS | 3.73 (2.25) | 4.33 (1.99) | 0.433 [†] |
| GENDER | 6 F 9 M | 6 F 9 M | 1.000 |
| MEDS | 12 | 11 | 0.679 |
| LENGTH | 419.7 (591.8) | 545.3 (513.4)* | 0.548 |

Abbreviations: MMSE= Mini mental state examination, YRS ED= years of education, GDS = Geriatric Depression scale, M=male, MEDS= participant taking prescribed antideementia medication (cholinesterase inhibitors or memantine). LENGTH= length of illness, measured in days from date of diagnosis to inclusion in study. *n=14. [†]Mann-Whitney U and Wilcoxon W Tests, due to non parametric data.

Fig. DS1 Examples of span trial types. A) Structured trial B) Random trial for both verbal and spatial span tasks:

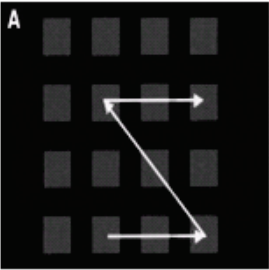
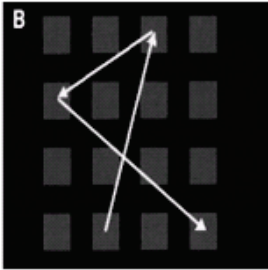
| Verbal Span Sequences | Spatial Span Sequences |
|---|--|
| <p>A) 2 4 6 9 7 5</p> <p>B) 8 1 6 2 9 4</p> |   |

Fig. DS2 Flow chart of recruitment.

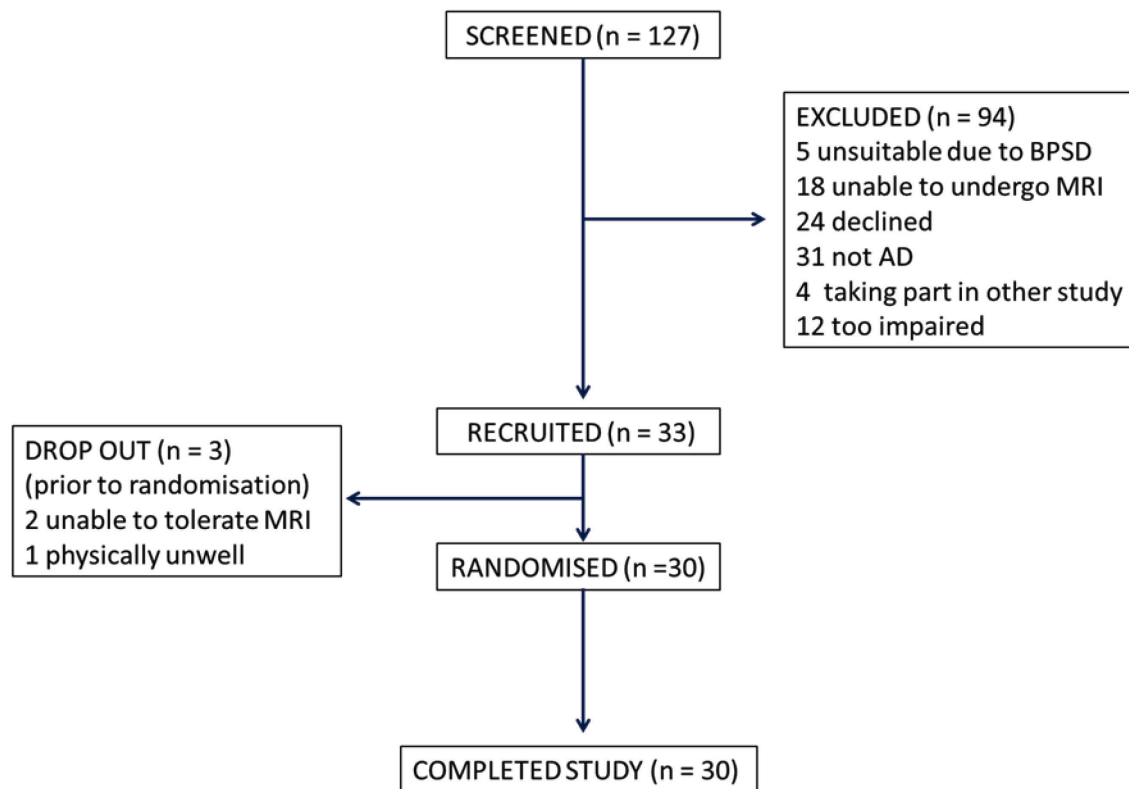


Fig. DS3 Mean fMRI response (parameter estimates) for A) Right dorsolateral prefrontal cortex B) Left dorsolateral prefrontal cortex regions of interest. CONT= control group, TRAIN = training group, PRE= pre intervention, POST = post intervention. Black bars = structured trials, White bars= random trails, Error bars are SEM

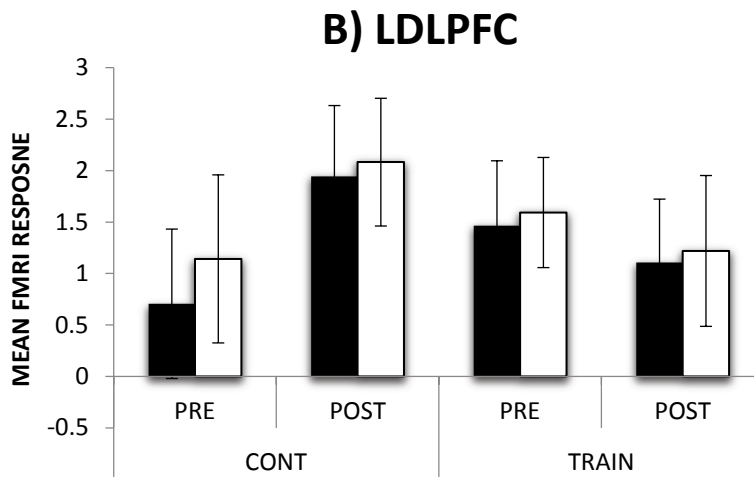
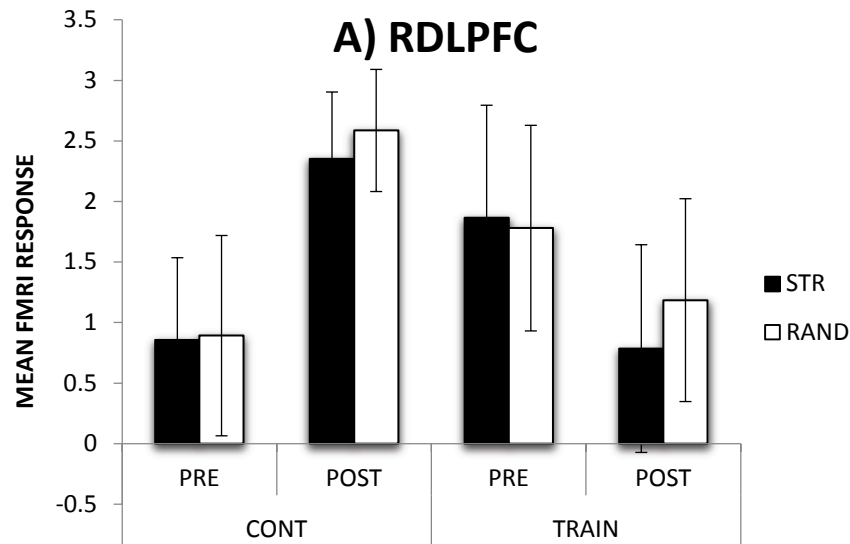
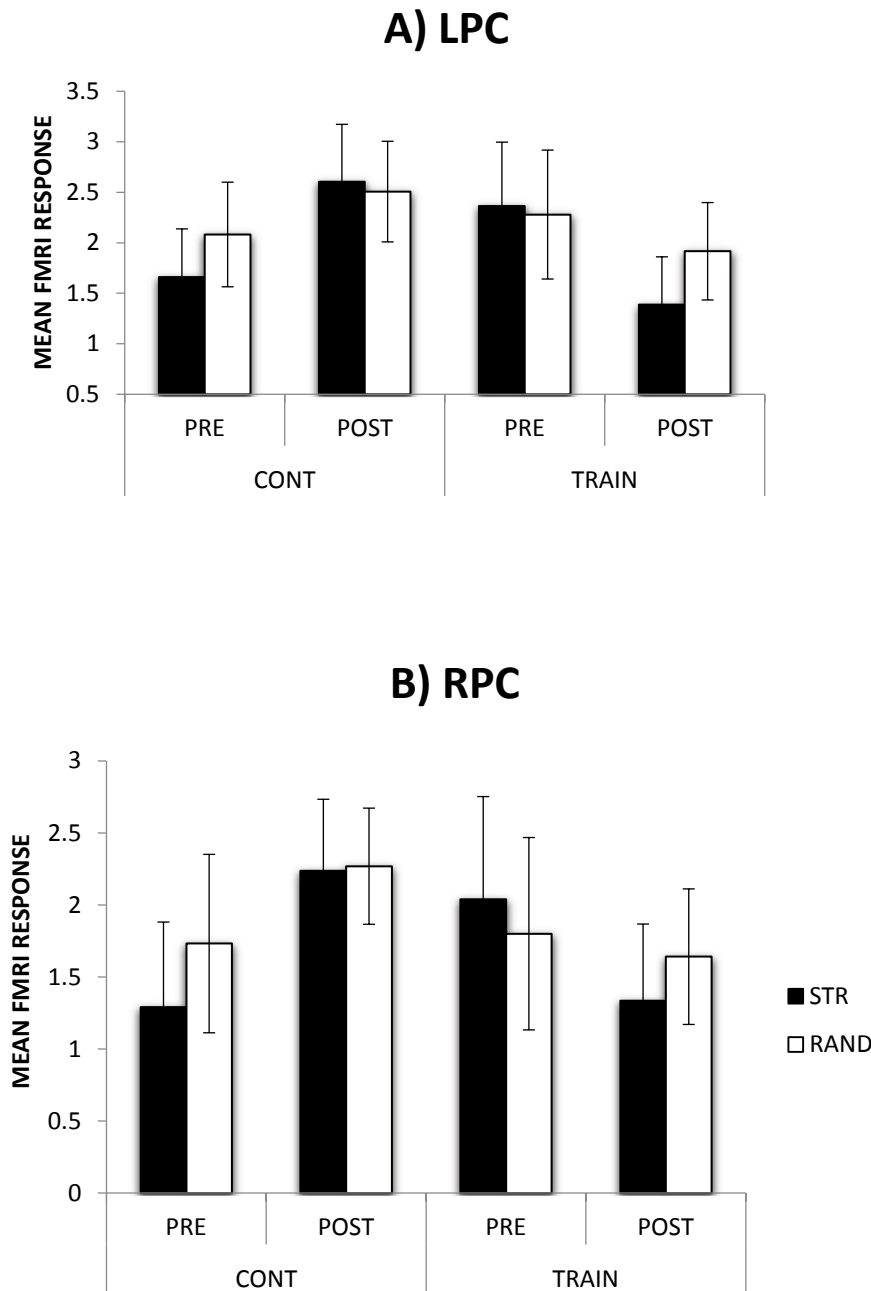


Fig. DS4 Mean fMRI response (beta values) for A) Left parietal cortex B) Right parietal cortex regions of interest. CONT= control group, TRAIN = training group, PRE= pre intervention, POST = post intervention. Black bars = structured trials, White bars= random trials, Error bars are SEM



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